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Estimating Causal Effects of Long-Term $PM_{2.5}$ Exposure on Mortality in New Jersey

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Short running title: Causal effects of long-term $PM_{2.5}$ on mortality

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Abstract

Background: Many studies have reported the associations between long-term exposure to $PM_{2.5}$ and increased risk of death. But, to our knowledge, none of them have used causal modeling approach or controlled for long-term temperature exposure. Few have used a general population sample.

Objective: We estimated the causal effects of long-term $PM_{2.5}$ effect on mortality and tested the effect modifications by seasonal temperatures, census-tract-level socio-economic variables, and county-level health conditions.

Methods: We applied a variant of the difference-in-differences approach, which serves to approximate random assignment of exposure across the population and hence estimate a causal effect. Specifically, we estimated the association between long-term exposure to $PM_{2.5}$ and mortality controlling for geographical differences using dummy variables for each census tract in New Jersey, a state-wide time trend using dummy variables for each year from 2004 to 2009, and mean summer and winter temperatures for each tract in each year. This approach assumed that no variable changing differentially over time across space other than seasonal temperatures confounded the association.

Results: For each interquartile range (2 $\mu g/m^3$) increase in annual $PM_{2.5}$, there was a 3.0% (95% confidence interval: 0.2, 5.9%) increase in all natural cause mortality for the whole population, with similar results for people older than 65 [3.5% (0.1, 6.9%)] and people 65 or younger [3.1% (-1.8, 8.2%)]. Mean summer temperature and mean winter temperature in a census tract significantly modified the effect of long-term exposure to $PM_{2.5}$ on mortality. We observed a higher percentage increase in mortality associated with $PM_{2.5}$ in census tracts with more blacks, lower home value, or lower median income.

Conclusions: Under the assumption of the difference-in-differences approach, we identified a causal effect of long-term $PM_{2.5}$ on mortality which is modified by seasonal temperatures and ecological socio-economic status.

Introduction

Many studies have reported the association of long-term exposure to fine particulate matter ($PM_{2.5}$) with mortality by following cohorts of subjects over time (Dockery et al. 1993; Beelen et al. 2008; Jerrett et al. 2013; Krewski et al. 2009; Lepeule et al. 2012; Pope et al. 1995; Puett et al. 2009). Initial studies, the Harvard Six Cities (HSC) and American Cancer Society (ACS) study, contrasted exposure across cities of residence (Dockery et al. 1993; Pope et al. 1995), and, more recently, land use regression has been used to assign exposure, such as in the ACS Cancer Prevention II study (CPS-II) and the Nurses' Health Study (NHS) (Jerrett et al. 2013; Puett et al. 2009).

However, a number of issues remain unresolved. First, the cohorts were convenience samples, which are not representative of the population as a whole, and often underrepresent minorities. For example, both the ACS cohort and the NHS cohort examine populations with considerably higher education than average (Pope et al. 1995; Puett et al. 2009). In addition, most cohorts (HSC, ACS, CPS-II, NHS) restricted the study population to city dwellers (Jerrett et al. 2013; Krewski et al. 2009; Lepeule et al. 2012; Puett et al. 2009), raising further issues about generalizability to the whole population. Secondly, temporal resolution of exposure has been limited. Since many land use regression models rely on extensive monitoring in a single year (Henderson et al. 2007; Hoek et al. 2008) to supplement routine monitoring, they are only

capable of estimating exposure for one year, which is taken as typical. Hence, only spatial variations in exposure can be used. In other studies, which used routine monitoring (Lepeule et al. 2012; Miller et al. 2007; Pope et al. 2009), lack of monitoring for $PM_{2.5}$ likewise limits exposure contrasts to geographic ones because the $PM_{2.5}$ level at the nearest monitoring site was assigned and often only a few monitoring sites were available for each city. This makes control for geographic confounders critical in all of these studies.

Further, causal modeling approach has not been used to estimate the effect of long-term exposure to $PM_{2.5}$ on mortality. To estimate causal effects, we need a counterfactual framework. Causal modeling seeks to estimate the difference in the expected value of mortality in the population under the exposure they received versus what it would have been had they received an alternative exposure. Since that counterfactual cannot be observed, various methods seek legitimate surrogates for the unobserved potential outcome. Randomized trials are one approach, but are not feasible for environmental exposures. Causal methods in observational epidemiology seek alternative ways to estimate a substitute for the counterfactual outcome (Baiocchi et al. 2014; Hernan et al. 2008; Rubin 1997). One approach uses formal modeling, such as inverse probability weighting and propensity scores, to make the exposure independent of all measured predictors, and relies on the untestable assumption of no unmeasured confounding (Cole and Hernan 2008; Stampf et al. 2010). The other approach relies on natural experiments or "random

shocks" which are used as instrumental variables. The variation in such an instrumental variable is a subset of the variation in exposure which is believed to be independent of measured and unmeasured confounders. However, the assumption that the exposure variation due to the instrumental variable are randomly assigned with respect to all measured or unmeasured confounders is untestable and often relies on external information to justify. When using natural experiments or "random shocks", some studies made use of the temporal variation in exposure caused by the "random shock". For example, Clancy et al. (2002) compared the mortality rate before (1984-1990) and after (1990-1996) the ban on coal sales in Dublin (Clancy et al. 2002). The ban is an instrumental variable that is related to a substantial reduction in air pollution after the implementation. It is likely that the ban or a change in policy is independent of measured or unmeasured variables that confound the association between air pollution and mortality. Some other studies relied on the spatiotemporal variation in exposure caused by the instrumental variable. An example is the difference-in-differences approach. For example, Card and Krueger evaluated the difference in fast food employment in New Jersey between February 1992 (two months before an increase in the minimum wage) and November 1992 (five months after the increase), and compared it to the difference in fast food employment between February and November 1992 in Pennsylvania, a neighboring state that did not change its minimum wage (Card and Krueger 1994). The increase in the minimum wage was a random shock. In other words, they estimated the difference in the change (difference) in employment over time between

the two states. Measured or unmeasured factors that might confound the association between the minimum wage and fast food employment at each point in time (e.g., education) might vary between the two states, but as long as any temporal variation in such factors was comparable between the states, they would not confound the difference in the change in employment over time between the states. Therefore, if the untestable assumption that the change in the minimum wage was the only factor influencing the difference in the rate of change in fast food employment between New Jersey and Pennsylvania is true, the difference in differences is unconfounded.

In this paper, we describe a variant of the differences-in-differences approach to estimate the causal relationship between annual average $PM_{2.5}$ and mortality in over 1900 census tracts within New Jersey during 2004–2009.

Methods

Mortality data

Death certificates in New Jersey from 2004 to 2009, including age, race, and the census tract of residence at the time of death for each individual, were obtained from the New Jersey Department of Health (NJDOH 2013). We only considered all natural cause deaths. People who died of external causes including injuries and poisoning were excluded [i.e. *International Statistical Classification of Diseases, 10th Revision* (ICD-10) codes S00 through U99]. We

regarded census tract as the unit of the analysis, aggregated annual natural cause death in each of the census tracts.

Exposure assessment

The exposure assessment was based on a previously published hybrid model incorporating daily satellite remote sensing data at 1 × 1 km spatial resolution (Kloog et al. 2014a). Briefly, we made use of a new algorithm developed by NASA - MAIAC (Multi-Angle Implementation to Atmospheric Correction). The MAIAC algorithm provides aerosol optical depth (AOD) data which allows us to use high resolution 1 × 1 km (versus currently available 10 km) AOD data. $PM_{2.5}$ was predicted using a mixed model with AOD, spatial and temporal predictors including meteorology, land use, and point emission. For the whole prediction area, the northeastern US, the mean out-of-sample R^2 from ten-fold cross-validation and slope of predictions were 0.88 and 0.99, respectively, suggesting excellent prediction ability. Annual $PM_{2.5}$ of a census tract in a given year was computed by averaging the predicted daily $PM_{2.5}$ over all 1 × 1 km grids within that census tract in that year.

Temperature

Daily mean air temperature at each 1 × 1 km grid in New Jersey was estimated using a similar mixed, spatio-temporal-resolved, and satellite-based model with MODIS measured surface temperature in 1 × 1 km spatial resolution (Kloog et al. 2014b). For the whole prediction area,

the northeastern US, the mean out-of-sample R^2 from ten-fold cross-validation was 0.95 when surface temperature was available and 0.94 when surface temperature was not, suggesting excellent prediction performance. More details have been published elsewhere (Kloog et al. 2014b). The mean summer temperatures of a census tract in a given year was computed by averaging the daily predicted air temperature from June to August in that year over all 1 × 1 km grids within that census tract, and the mean winter temperatures were the averages in January, February, and December. We controlled for the mean summer and winter temperatures when estimating the association between $PM_{2.5}$ and mortality. These two variables were also tested as potential effect modifiers.

Socio-economic and behavioral data

From the US Census for 2000, summary file 3, we obtained census-tract-level data on population, socio-economic status (SES) including percent of black residents, median household income, and median value of owner occupied homes (U.S. Census Bureau 2000). We also obtained age-adjusted yearly prevalence estimates of diabetes and smoking at county level from 2004 to 2009 from the CDC Behavioral Risk Factor Surveillance System (BRFSS) (CDC 2013).

Difference-in-differences approach

We begin with the potential outcomes framework of the Rubin Causal Model (Rubin 1991). Let $Y_{c,t}^{A=a}$ be the potential outcome (aggregated number of deaths) in the population of census tract c

if exposed to A=a in year t, and let $Y_{c,t}^{A=a'}$ be the potential outcome under the alternative exposure a′. We would like to estimate $E\left(Y_{c,t}^{A=a}\right)/E\left(Y_{c,t}^{A=a'}\right)$. We assume that the potential outcome depends on predictors in the following manner:

$$\log(E(Y^{a}_{c,t})) = \beta_0 + \beta_1 a + \beta_2 Z_c + \beta_3 U_t + \beta_4 W_{c,t} + \log(P_c) \quad [1]$$

where Z_c are spatial confounders that vary among census tracts but not over the time period of the study (e.g., SES and diet), U_t are temporal confounders that vary over time but not among census tracts, $W_{c,t}$ are confounders that vary over time and among census tracts, and $\log(P_c)$ is an offset term representing the natural log of the population in census tract c.

Although equation 1 uses the aggregated number of deaths in a census tract in a year (in an ecological form), it closely relates to an individual-level model. Ecological bias is a potential concern when non-linear dose-response relationship and within-area variability exist, because an individual risk model may have a different form from the ecological model (Jackson et al. 2006). However, as shown by Lu and Zeger (2007), a model of aggregated event counts can be derived from an individual risk model when the exposure is common across individuals (Lu and Zeger 2007), as was the case for the present study, where $PM_{2.5}$ for each individual during each year was assigned as the average value over all 1 × 1 km geographic grids within their census tract in that year. Although such assignment introduces Berkson error in exposure assessment, it will not bias the effect estimates.

Specifically, for individual i in census tract c in year t, the risk of death (λ) could be modeled as,

$$\lambda_{ci}(t, PM_{cit}) = \lambda_{0ci}(t) \exp(\beta_1 PM_{cit}) = \lambda_{0ci} \exp(\beta_1 PM_{cit} + \gamma_{cit}). \quad [2]$$

where λ_0 represents the baseline risk of mortality, and γ represents the individual-level confounders. Using the condition that $PM_{cit} = PM_{ct}$,

$$\lambda_{ci}(t, PM_{cit}) = \lambda_{0ci} \exp(\beta_1 PM_{ct} + \gamma_{cit}). \quad [3]$$

This step introduces Berkson error. Then we sum up both sides of equation [3] over all of the subjects in tract c and year t,

$$\mu_{ct} = \Sigma_i \lambda_{0ci} \exp(\beta_1 PM_{ct} + \gamma_{cit}) = \exp(\beta_1 PM_{ct}) \times \Sigma_i \lambda_{0ci} \exp(\gamma_{cit}) = \exp(\beta_1 PM_{ct} + \log(\Sigma_i \lambda_{0ci} \exp(\gamma_{cit}))) \quad [4]$$

where μ_{ct} is the expected mortality in tract c in year t. Since $\log(\Sigma_i \lambda_{0ci} \exp(\gamma_{cit}))$ is a function of t in tract c, we have

$$\mu_{ct} = \exp(\beta_1 PM_{ct} + f_c(t)), \quad [5]$$

where $f_c(t)$ is a function of time for each census tract that could be decomposed into a tract-specific component that is constant over time (Z_c), a time-varying component that is homogeneous over all tracts (U_t), and a component that varies over time and among census tracts ($W_{c,t}$), which is essentially the same as equation 1.

Then let us look at equation 1 again. If we look at differences between adjoining years, where the exposure in the other year is a′, we have:

$$\log\left(E\left(Y_{c,t}^{a}\right)\right) - \log\left(E\left(Y_{c,t-1}^{a'}\right)\right) = \beta_1(a - a') + \beta_3(U_t - U_{t-1}) + \beta_4\left(W_{c,t} - W_{c.t-1}\right) \quad [6]$$

and Z_c and β_0 have disappeared. If we then take the difference of these differences between census tracts c and c′, we have

$$\left[\log\left(E\left(Y_{c,t}^{a}\right)\right) - \log\left(E\left(Y_{c,t-1}^{a'}\right)\right)\right] - \left[\log\left(E\left(Y_{c',t}^{b}\right)\right) - \log\left(E\left(Y_{c',t-1}^{b'}\right)\right)\right]$$
$$= \beta_1[(a - a') - (b - b')] + \beta_4\left[\left(W_{c,t} - W_{c.t-1}\right) - \left(W_{c\prime,t} - W_{c\prime.t-1}\right)\right] \quad [7]$$

where b and b′ are the exposures in tract c′ at times t and t-1, respectively. If the change in $W_{c,t}$ over a year is the same in both locations, then $\left(W_{c,t} - W_{c.t-1}\right) - \left(W_{c\prime,t} - W_{c\prime.t-1}\right)$ is zero and the difference between locations in these within location differences will only depend on the difference in their exposure differences, and hence this estimate will be causal. It is also a marginal, not conditional, estimate since it is not conditioned on Z_c, U_t, and $W_{c,t}$. Alternatively, if differences in the rate of change of the $W_{c,t}$ are uncorrelated with differences in the rate of change of exposure in different locations, then the results are still causal. This is the key assumption of this approach. The advantage of this approach is, when this assumption holds, the ability to control for unmeasured confounders (Z_c, U_t, and $W_{c,t}$ need not be observed, since they cancel out).

We can generalize this to include many census tracts instead of two, and to include six years instead of two, and to deal with nonlinear changes over time. Estimating differences between years (equation [6]) removes confounding by variables that vary by census tract but not time (Z_c). In the context of multiple tracts, we can accomplish this by controlling for indicator variables for each tract. Estimating differences between census tracts (equation [7]) removes confounding by covariates that vary over time, but are constant between census tracts (U_t). Again, using indicator variables for each of the six years accomplishes the same thing, even if the trend over time is not linear. More formally, from equation 1, we have

$$\log\left(E\left(Y_{c,t}^{a}\right)\right) = \beta_0 + \beta_1 a + \beta_2 Z_c + \beta_3 U_t + \beta_4 W_{c,t} + \log P_c$$

$$= \beta_0 + \beta_1 a + \sum_{c \neq c_R} \beta_2 Z_c I_c + \sum_{t \neq t_R} \beta_3 U_t I_t + \beta_4 W_{c,t} + \log P_c$$

$$= \beta_0 + \beta_1 a + \sum_{c \neq c_R} \beta_c I_c + \sum_{t \neq t_R} \beta_t I_t + \beta_4 W_{c,t} + \log P_c \qquad [8]$$

where I_c and I_t (indicator variables for tract c and year t, respectively) effectively control for Z_c and U_t under multi-tract and multi-year scenarios, in the same way that the differencing in equations 6 and 7 control for Z_c and U_t when there are only two tracts and two years. β_c is the time-invariant component for tract c and β_t is time trend for year t. We used c_R to denote the reference census tract and t_R to denote the reference year. In summary, spatial and temporal confounders are controlled because differences among census tracts and time trends are

controlled by I_c and I_t, and there is no confounding by person-specific factors that vary within years and census tracts because all persons in a census tract during a given year have the same exposure.

For the above to be a causal estimate, we must also assume that differences in the $W_{c,t}$ from the tract level mean (captured by the dummy variable for tract) and state level trend are uncorrelated with the same differences in exposure. This is the untestable hypothesis, which must be judged on external information. How plausible is it? Factors such as SES and smoking rate vary across census tracts in New Jersey, and it is possible that these variations might be correlated with air pollution. But all differences between census tracts in any such variables are removed by using a dummy variable for each tract. What remains is variation in, for example, smoking rates that varied differentially among census tracts and over time. These would have to be correlated with variations in $PM_{2.5}$ from its census tract average and mean yearly change in New Jersey for confounding to remain. This seems much less plausible. Indeed, these tract specific pollution changes mostly depend on EPA regulatory changes, and on year-to-year variations in back trajectories (more or less polluted areas upwind), mixing height, and other meteorological factors which are unlikely to be related to smoking or any other covariate over this six-year time period, except temperature. Therefore, to account for potential confounding by temperature, we adjust

for functions of temperatures, as shown in equation 9 where the difference-in-differences approach is modeled using Poisson regression with overdispersion (Donohue and Ho 2007):

$$\log\left(E\left(Y_{c,t}\right)\right) = \beta_0 + \beta_1 \mathrm{PM}_{c,t} + \sum_{c \neq c_R} \beta_c \mathrm{I}_c + \sum_{t \neq t_R} \beta_t \mathrm{I}_t + \mathrm{s}\left(Ts_{c,t}; \boldsymbol{\beta_{Ts}}\right) + \mathrm{s}\left(Tw_{c,t}; \boldsymbol{\beta_{Tw}}\right) + \log P_c \quad [9]$$

where $\mathrm{PM}_{c,t}$ is $\mathrm{PM}_{2.5}$ concentration in tract c at time t, I_c and I_t represent indicators for each census tract and year, and $\mathrm{Ts}_{c,t}$ and $\mathrm{Tw}_{c,t}$ represent mean summer and winter temperatures for each tract and year, which are modeled as linear splines (function s) with a single knot at their means to account for possible nonlinear associations of temperature with mortality. Seasonal temperatures are linked to mortality (Shi et al. 2015) and could also be related to aerosol concentration (Rosenfeld et al. 2014). Since an increase in temperature in the winter may have a different effect (and sign) on mortality than an increase in the summer, we chose to use the mean summer and mean winter temperature as two weather-related variables (as opposed to annual mean temperature) that may influence annual mortality rates (Shi et al. 2015). To summarize, the difference-in-differences approach controlled for (1) geographical differences using dummy variables for each tract; (2) a state-wide time trend using dummy variables for each year; and (3) variables that vary differentially over time and across space that is correlated with $\mathrm{PM}_{2.5}$ which are seasonal temperatures. For the estimate to be causal, we assume that no variable that changes

differentially among space and over time other than temperature confounds the association between the exposure and the outcome.

The difference-in-differences approach was applied to estimate the causal effect of long-term exposure to $PM_{2.5}$ on mortality among people in New Jersey. We also estimated the association for people aged >65 years old and people aged 65 or younger by stratification. We tested if the association was modified by mean summer temperature and mean winter temperature. We achieved this by adding into the model two sets of product terms: one is the product terms between the spline of mean summer temperature and $PM_{2.5}$ and the other is the product terms between the spline of mean winter temperature and $PM_{2.5}$. We also tested if the association was modified by ecological SES variables at census tract level using Census 2000 data (the percent of black residents, median household income, and median home values), and ecological health condition at county level using BRFSS data during 2004-2009 (age-adjusted prevalence of diabetes and smoking). These effect modifications were tested by adding a product term between $PM_{2.5}$ and the modifier into the model. Not only did we test these effect modifications among the whole population, we also tested them in a subgroup analysis by restricting the study population to the white residents (70% of the total population) to see if the results are consistent within a race group. The consistency could reflect if the association estimated using the whole population was confounded by individual-level race group. We did not repeat the analysis for other race

groups due to insufficient power to detect effect modifications. In addition, because these effect modifiers all reflected the SES of a census tract and are potentially related to each other, we fitted a model with simultaneous interactions of $PM_{2.5}$ with percent of black residents, home value, household income, smoking rate, and diabetes rates to see which of them are the most robust modifiers. We used backward elimination to select the modifiers. Specifically, we started from a model with all five interaction terms. Then the interaction term with the largest p-value was dropped and a model without that interaction term was refitted. We repeated this procedure and stopped dropping variables until each of the remaining interaction terms has a p-value of <0.05.

To compare the difference-in-differences approach with an estimate derived using only the within-tract variation of the exposure, we performed a sensitivity analysis fitting Poisson regression within each of the census tracts regressing total mortality against $PM_{2.5}$, and pooled the effect estimates using random-effects meta-analysis.

All statistical analyses were done using R 3.1.2. Statistical significance was defined as p-value < 0.05.

Results

Using population counts from Census 2000 data, we studied 1,938 census tracts in New Jersey during 2004-2009. In total, there were 365,530 deaths from 2004 to 2009, among which 281,170

deaths were at age greater than 65, representing 77% of the total. Table 1 and table 2 summarize the spatial and temporal variation of mortality, $PM_{2.5}$ and temperature. The spatial variation of mortality is calculated by first averaging the annual deaths from 2004 to 2009 in each of the census tracts and then summarizing the distribution using these death counts. The spatial distribution of mortality had a mean of 31.4 deaths per year per census tract. Much of the variation in deaths was due to variations in the age distribution and size of the population in each tract. For example, the $5^{th} – 95^{th}$ percentile range in the annual mortality rate of persons over 65 across census tracts was from 22.1 to 62.8 per thousand. The $5^{th} – 95^{th}$ percentile range of averaged annual $PM_{2.5}$ over six years ranged from 9.9 to 12.9 $\mu g/m^3$ across census tracts with a mean of 11.3 $\mu g/m^3$. The $5^{th} – 95^{th}$ percentile range of mean temperature varied from 17.2 to 19.6 °C in summers, and from 4.6 to 7.0 °C in winters. The temporal trend is presented using the average of the variables over all of the census tracts in New Jersey in each year from 2004 to 2009. Mortality counts went down in 2006 and 2007 compared to 2004 and 2005, and but went slightly back up in 2008 and 2009, indicative of nonlinear or random pattern in temporal variation.

On the basis of the difference-in-differences approach (equation 9), we found a 3.0% [95% confidence interval 0.2, 5.9%] increase in all natural cause mortality for each interquartile range (IQR) increase in $PM_{2.5}$ (2 $\mu g/m^3$) among all residents in 1938 census tracts in New Jersey during

2004-2009. By comparison, the meta-analysis pooling all within-census-tract effects showed a similar increase of 3.7% (2.9, 4.5%) in mortality per IQR increase in $PM_{2.5}$. Restricting the study population to age of death greater than 65 years, we obtained a similar effect estimate: 3.5% (0.1, 6.9%) increase in mortality per IQR increase in $PM_{2.5}$. For people at age less than or equal to 65, the percent change in mortality was similar, 3.1% (-1.8, 8.2%), albeit with wider confidence interval.

The percent change in mortality with an IQR increase in $PM_{2.5}$ was 1.8% (95% CI: -1.6, 5.2%) if mean summer and winter temperatures were at the average across all tracts and years (Table 3). By comparison, the percent change in mortality with an IQR increase in $PM_{2.5}$ was -1.6% (-4.2, 1.1%) if mean summer temperature was 1 ˚C below the average across tracts and years and mean winter temperatures was at the average (interaction p-value <0.01) and was 1.6% (-0.6, 3.8%) if mean summer temperature was 1 ˚C above the average across tracts and years and mean winter temperature was at the average (interaction p-value 0.73). The percent change in mortality was 1.6% (-0.6, 3.9%) if mean winter temperature was 1 ˚C below the average across tracts and years and mean summer temperature was at the average (interaction p-value 0.82) and was 5.3% (2.9, 7.8%) if mean winter temperature was 1 ˚C above the average across tracts and years and mean summer temperature was at the average (interaction p-value <0.01).

Figure 1 shows the estimated effects per interquartile range increase in $PM_{2.5}$ on mortality rates in the upper and lower deciles of census-tract-level percent of black residents, median home value and median household income from Census 2000 data and age-adjusted diabetes and smoking rate from BRFSS data during 2004-2009. Among the whole population, the percent change in mortality associated with $PM_{2.5}$ was modified by the percent of black residents (interaction $p<0.01$), median income (interaction $p<0.01$), and home values (interaction $p = 0.02$). We did not find effect modifications by smoking rates (interaction $p = 0.60$) or percent of diabetics (interaction $p = 0.06$). Using backward elimination to select interaction terms from the simultaneous interaction model, we found that median household income was the only robust modifier that finally remained in the model. We also tested the consistency of these results among white residents (70% of the total population). We found that $PM_{2.5}$ significantly interacted with percent of black residents (interaction $p<0.01$), age-adjusted diabetes (interaction $p<0.01$), and median income (interaction $p<0.01$), but not with smoking rate (interaction $p = 0.63$), or median home value (interaction $p = 0.13$).

Discussion

The present study used a variant of difference-in-differences approach to estimate the causal effect of long-term exposure to $PM_{2.5}$ on mortality in a large and general population.

First, we have estimated the association between $PM_{2.5}$ and mortality using a counterfactual framework. We have accounted for SES, behavioral, and other risk factors that vary among census tracts by modeling dummy variables for each tract. We have limited potential changes over time in such risk factors by focusing on a short time period (six years), and by adjusting for average changes from year to year in New Jersey as a whole. If our assumption that yearly deviations from the state-wide yearly fluctuations in $PM_{2.5}$ by tract (mostly due to regulatory and meteorological fluctuations) are unlikely to be associated with changes in other risk factors holds, we have identified a causal association.

Second, the results add to the still relatively small literature that uses the general population which includes both high and low SES individuals, all occupations, and both rural and urban residents.

The third is that we have identified interactions between $PM_{2.5}$ and seasonal temperature. By far, very few studies have looked at the health effect of long-term temperature. An increase in mean summer temperature, a decrease in mean winter temperature, or an increase in the variability of summer or winter temperature were associated with a decrease in the hazard of death among Medicare beneficiaries in New England during 2000-2008 (Shi et al. 2015). There are also very few studies looking at the interaction between long-term temperature and long-term $PM_{2.5}$. A survival analysis among >35 million Medicare beneficiaries residing in 207 US cities during

2000-2010 found that an increase in annual, summer, or winter temperature was associated with an increase in the hazard ratio of death associated with $PM_{2.5}$ (Kioumourtzoglou et al. 2016). Consistently, we found that an increase in mean winter temperature was associated with an increase in the effect of $PM_{2.5}$ on mortality. With regard to summers, the association between an IQR increase in $PM_{2.5}$ and mortality in tracts with mean summer temperatures that are higher than the average are similar to the overall association. The interaction was driven more by a reduced risk of mortality in association with $PM_{2.5}$ when mean summer temperatures are lower than the average. Under the changing climate, a rise in temperature not only would increase mortality through the direct effects of temperature, but also would increase the effect of long-term $PM_{2.5}$ exposure on mortality.

The fourth is that by analyzing the population of an entire state we have had power to test interaction and found that the effect of $PM_{2.5}$ was higher in census tracts with higher percentage of black residents, lower median home value, or lower median home income. Median household income was the most robust variable among these three SES variables. All these analyses consistently suggested that the effect of $PM_{2.5}$ was higher in tracts with lower SES. Consistently, a recent study, Kioumourtzoglou et al. (2016), also found that a unit increase in $PM_{2.5}$ in cities with higher percentage of black or lower household income was associated with higher percent increase in mortality among >35 million Medicare beneficiaries residing in 207 US cities during

2000-2010 (Kioumourtzoglou et al. 2016). When restricting the analysis to the white residents, we found that the interactions were basically consistent compared to the analyses for the whole population. This suggests that the estimates obtained using the whole population for $PM_{2.5}$ were not confounded by individual-level race. The consistency between these two analyses also suggested that the SES of the neighborhood (or other people) would be associated with an individual's susceptibility, which is a contextual effect.

The fifth is that we identified this association in a location and time period with low concentrations of $PM_{2.5}$. The average $PM_{2.5}$ over the period of study was 11.3 $\mu g/m^3$, and the range across the census tracts was from 8.2 $\mu g/m^3$ to 13.7 $\mu g/m^3$. Hence, this association was estimated completely below the old EPA annual standard of 15 $\mu g/m^3$ (U.S. EPA, 1997), and predominantly below the current standard of 12 $\mu g/m^3$ (U.S. EPA, 2013).

To compare with previous studies, we converted the percent change in mortality from our study to reflect a 10 $\mu g/m^3$ increase. We found a 15.5% (0.8, 32.3%) increase in all natural cause mortality for the entire population in New Jersey. By comparison, the HSC study reported an estimate of 13% (4, 23%) and its extended study reported a 14% (7, 22%) increase in mortality (Dockery et al. 1993; Lepeule et al. 2012). The ACS cohort which examined the association among 500,000 residents residing in 51 cities found a 6% (2, 10%) increase in mortality (Pope et al. 1995; Pope et al. 2002). The NHS cohort which examined the association with all cause

mortality among women reported an increase of 26% (2, 54%) (Puett et al. 2009). Our result lied on the higher end compared with these cohort studies, possibly due to the fact that we used a spatially resolved exposure model. The NHS study which used geographically resolved exposure assessment also tended to have a larger effect size (Puett et al. 2009). Further, our model has a higher cross-validation R^2 than most land use regression models. Hoek et al. (2008) summarized a number of land use regressions. The highest R^2 of the model (typically higher than the cross-validation R^2) was 0.82. It is typical to have a R^2 of model below 0.7 (Hoek et al. 2008). The land use regression used in the NHS study had a cross validation R^2 of 0.77 and 0.69 for post- and pre-1999 periods (Yanosky et al. 2009). By comparison, our model had a cross-validation R^2 of 0.88, which produced exposure predictions with less measurement error. We found that the percent change in mortality among people over 65 years in age in New Jersey was 18.1% (0.6, 38.6%) for each 10 $\mu g\ m^{-3}$ increase in long-term $PM_{2.5}$. This estimate is larger than the estimate, 4% (3, 6%) increase in all cause mortality, among Medicare beneficiaries residing in 4,568 zip codes (people aged 65 or above) during 2000-2005 (Zeger et al. 2008), which used average $PM_{2.5}$ concentrations measured by monitors within six miles from a zip code to approximate exposure. A lower exposure measurement error may be one of the reasons why our study found a larger effect of $PM_{2.5}$. The sensitivity analysis (meta-analysis pooling within-census-tract effects) found a 3.7% (2.9, 4.5%) increase in mortality per IQR increase in $PM_{2.5}$, suggesting our result was close to the result using within-census-tract analysis.

We acknowledge that our study has limitations. First, we did not control for some of the differential changes over time across census tracts. Although temperature may be the strongest confounder between $PM_{2.5}$ and mortality, the change over time in other variables such as the employment rates may also confound the relationship. Second, we did not measure individual-level predictors of mortality. Variations in these predictors within a census tract, however, cannot confound $PM_{2.5}$ since they are not correlated with exposure (everyone in the tract has the same exposure in the same year). They cannot confound associations between census tracts, because there is no exposure contrast between tracts (due to the dummy variables for each tract). And they cannot confound over time because dummy variables for each year remove that pattern from outcome and exposure. For them to confound, their difference from the general trend by tract would have to be correlated with the differences around the trend in $PM_{2.5}$, and we can see no mechanism that would produce this correlation. Although variations in the individual-level predictors cannot confound the association, we acknowledge that the exposure misclassification occurs from assigning the same yearly averaged $PM_{2.5}$ in census tracts for all residents. This variation in exposure for each individual around a small area should be Berksonian, which should not bias our estimates, but will increase the confidence intervals. By comparison, cohort studies assigning exposure for each of the subjects according to the date of death will not suffer from this problem if they have address-specific exposure. Moreover, our modeling does not fall into the typical ecological bias in which the exposed may not be the ones who developed the

outcome, since everyone within a census tract was assigned to the same geographically averaged exposure. Third, using $PM_{2.5}$ at census tract level to assess the exposure is still not as accurate as using $PM_{2.5}$ predictions at the address level. Fourth, in our analysis, the strong control for spatial confounding and temporal trend using dummy variables for each census tract and each year substantially lowered the exposure contrast across tracts and over time, which potentially increased the standard error of effect of $PM_{2.5}$. Fifth, the population in each census tract was likely to change from 2004 to 2009. Our analyses used population data from Census 2000 to approximate the population in 2004-2009 which possibly added inaccuracy to the estimates.

Conclusions

Under the assumption that no variable changing differentially over time across census tracts other than seasonal temperatures could confound the association, we found causal associations between $PM_{2.5}$ and all natural cause mortality. The effect estimates of $PM_{2.5}$ from our analyses were comparable to previous cohort studies, but on the higher end. The association was modified by seasonal temperatures and ecological SES variables.

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Table 1. Distribution of census-tract-specific mean values for 2004 through 2009 for annual all natural cause mortality, annual mean $PM_{2.5}$, mean summer temperature, and mean winter temperature among 1,938 census tracts in New Jersey.

Variable	Mean	5th	25th	Median	75th	95th
Death counts per census tract per year (All age groups)	31.4	7.7	17.8	27.0	39.8	70.0
Mortality rate (All age groups, per 1,000)	7.3	3.0	4.9	6.6	8.5	13.6
Population (All age groups, based on Census 2000 data)	4,412	1,853	3,152	4,181	5,562	7,527
Death counts per census tract per year (Age > 65)	24.2	4.3	12.5	19.5	30.3	58.7
Mortality rate (Age > 65, per 1,000)	40.1	22.1	31.2	38.5	47.2	62.8
Population (Age > 65, based on Census 2000 data)	598	175	350	525	756	1,207
Death counts per census tract per year (Age ≤ 65)	7.2	2.0	4.5	6.7	9.3	14.8
Mortality rate (Age ≤ 65, per 1,000)	2.1	0.8	1.3	1.8	2.4	4.2
Population (Age ≤ 65, based on Census 2000 data)	3,814	1,535	2,712	3,639	4,868	6,555
Annual $PM_{2.5}$ ($\mu g\ m^{-3}$)	11.3	9.9	10.8	11.2	11.9	12.9
Summer temperature[a] (°C)	18.6	17.2	18.2	18.7	19.1	19.6
Winter Temperature[a] (°C)	5.9	4.6	5.6	5.9	6.2	7.0

[a]Summer (winter) temperature is an average of the predicted daily temperatures across all 1 km × 1 km grids in a given census tract during June, July, and August (January, February, and December) in a given year.

Table 2. Annual mean values (± SD) across 1,938 New Jersey census tracts for all natural cause mortality, annual mean $PM_{2.5}$, mean summer temperature, and mean winter temperature.

Variable	2004	2005	2006	2007	2008	2009
Death counts per census tract per year (All age groups)	34.3 ± 23.9	34.2 ± 23.7	29.2 ± 22.5	28.7 ± 21.6	30.2 ± 21.3	32.0 ± 22.6
Death counts per census tract per year (Age > 65)	26.4 ± 21.2	26.5 ± 21.0	22.2 ± 19.8	22.2 ± 19.1	23.2 ± 19.1	24.6 ± 20.2
Death counts per census tract per year (Age ≤ 65)	7.9 ± 5.4	7.7 ± 5.2	7.0 ± 5.1	6.6 ± 4.7	7.0 ± 4.6	7.4 ± 4.7
Annual $PM_{2.5}$ ($\mu g/m^{-3}$)	12.3 ± 1.0	12.8 ± 1.2	11.7 ± 0.9	11.6 ± 1.0	10.6 ± 0.8	9.1 ± 0.7
Summer temperature[a] (°C)	18.1 ± 0.6	20.3 ± 0.8	19.1 ± 0.7	18.4 ± 0.7	18.6 ± 0.8	17.3 ± 0.7
Winter temperature[a] (°C)	4.3 ± 0.7	5.0 ± 0.7	7.8 ± 0.6	5.9 ± 0.7	6.7 ± 0.7	5.7 ± 0.8

[a]Summer (winter) temperature is an average of the predicted daily temperatures across all 1 km × 1 km grids in a given census tract during June, July, and August (January, February, and December) in a given year.

Table 3. Percent change (95% CI) in mortality per IQR increase (2 μg m^{-3}) increase in PM2.5 at given summer and winter temperature.

Mean Summer Temperature (˚C)	Mean Winter Temperature (˚C)	Percent Change (95% CI) in Mortality Per IQR Increase in $PM_{2.5}$
18.6[a] (Average)	5.9[b] (Average)	1.8% (-1.6, 5.2%)
17.6 (Average - 1)	5.9 (Average)	-1.6% (-4.2, 1.1%)
19.6 (Average + 1)	5.9 (Average)	1.6% (-0.6, 3.8%)
18.6 (Average)	4.9 (Average - 1)	1.6% (-0.6, 3.9%)
18.6 (Average)	6.9 (Average + 1)	5.3% (2.9, 7.8%)

[a]the average of the census-tract-specific mean summer temperature across 1,938 census tracts during 2004-2009.

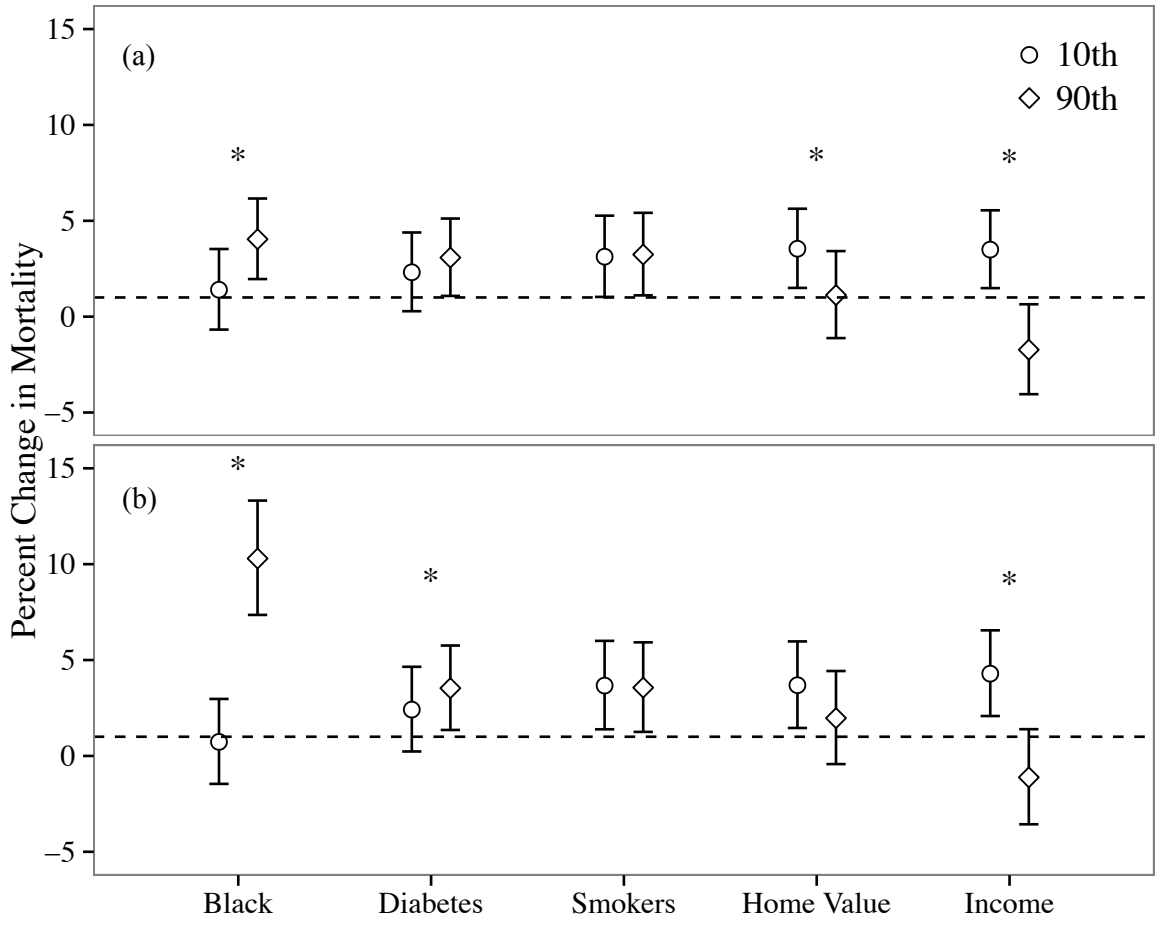
[b]the average of the census-tract-specific mean winter temperature across 1,938 census tracts during 2004-2009.

Figure Legend

Figure 1. Percent change in mortality with 95% confidence intervals for each interquartile range (2.0 μg/m^3) increase in $PM_{2.5}$ at the upper and lower decile of each modifier: percent of black residents (10^{th} percentile = 0.2%, 90^{th} percentile = 52.0%) , percent of diabetics (10^{th} percentile = 6.1%, 90^{th} percentile = 9.2%), smoking rate (10^{th} percentile = 7.8%, 90^{th} percentile = 15.9%), median home value (10^{th} percentile = 189,300, 90^{th} percentile = 578,600), and median household income (10^{th} percentile = 35,625, 90^{th} percentile = 115,049) among (A) the whole population and (B) the white residents in New Jersey. Census-tract-specific percent of black residents, median home value, and median household income came from Census 2000 data. County-level percent diabetics and smoking rate came from BRFSS data from 2004 to 2009.

* indicates interaction $p < 0.05$.

Figure 1


(a)
(b)
10th
90th
Percent Change in Mortality
15
10
5
0
−5
*
Black
Diabetes
Smokers
Home Value
Income